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10/826,113	04/16/2004	Piotr Chomczynski	CNA / 19	1054

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/826,113	CHOMCZYNSKI, PIOTR	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-39,41,44,46-52 and 59-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *44,62 and 63* is/are allowed.

6)☒ Claim(s) *29-39,41,46-52 and 59-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Interpretation

1. Prior to application of the art, the scope and content of the claims must be analyzed. In this case, the new limitation to require "a buffer at a concentration sufficient to maintain a pH in the range from about pH 3.6 to below pH 4.0" does not provide any specific requirements for the buffer. Therefore, any amount of buffer will function to maintain the pH in the desired range when the sample is already in the desired range. Consequently, this limitation does not necessarily impose any limitation on the claim other than the presence of a component with even minimal buffering capacity. For purposes of compact prosecution, both anticipatory and obviousness rejections will be made over this limitation, in order to fully address the limitation.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 29-39, 41, 46-52 and 59-61 are rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al (Chinese patent 1,220,995, translation).

The rejection is based upon a translation of the Chen et al patent, which is attached.

Chen teaches a *method for isolating purified RNA from a biological sample* of claims 29 and 59 (see page 3, bottom half, for example or page 4) comprising:

a) *treating the sample comprising phenol at a final concentration ranging from about 10% w/w to about 60% w/w and at least one ribonuclease inhibitor* (see page 6, where 12-46% phenol is used in conjunction with guanidine isothiocyanate, an RNAse inhibitor and see page 8, preferred embodiment 2, step 1, where the phenol reagent with 30% w/w is added to the tissue),

b) mixing the sample with at least one hydrophobic solvent and a buffer at a concentration sufficient to maintain a pH in the range from about pH 3.6 to below pH 4.0 (see page 8, preferred embodiment 2, where the pH of the phenol reagent is pH 3.5, which is about 3.6 and where the hydrophobic solvent chloroform/isoamyl alcohol is added to the solution. Further note that Chen teaches overlapping ranges of pH from 3.5 to 6.5 and the use of glacial acetic acid to regulate the pH value (see page 3)),

c) recovering the purified RNA from an aqueous phase to which about an equal volume of a water soluble organic solvent is added to precipitate the purified RNA (See page 8, preferred embodiment 2, where the aqueous phase is precipitated with isopropanol),

d) washing and solubilizing the precipitated RNA (see page 9, where the RNA precipitate is washed with alcohol and dissolved in a buffer).

With regard to claim 30, Chen teaches the use of acetate and citrate buffers (see page 8, preferred embodiment 2, lines 3 and 4).

With regard to claims 31-34, Chen teaches the use of ribonuclease inhibitors (see page 8, preferred embodiment 2, line 1, where the chaotropic salt guanidine

isothiocyanate is used as an RNAse inhibitor at a concentration in the range of 0.5 M to about 6M).

With regard to claims 35-36, Chen teaches the use of detergents such as SDS and sarcosine including a range of 0.1% SDS (see page 8, preferred embodiment 2, lines 2-3).

With regard to claims 37-39, Chen teaches the use of sodium acetate and trisodium citrate, where claim 38 indicates that acetate is a preferred salt and claim 39 indicates that citrate is a preferred chelating agent).

With regard to claim 41, Chen teaches the use of Guanidine salts (see page 8, line 1).

With regard to claims 46, Chen teaches a pH range of 3.5-6.5 and exemplifies a pH of 3.5 (see page 3 and see page 8, preferred embodiment 2).

With regard to claims 47-49, Chen teaches the steps of:

a) treatment with the monophase reagent comprising phenol in concentrations from 12-46% w/w (see page 6) with a pH from 3.5-6.5 (see page 3) and a chaotrope (see page 6 where guandine isothiocyanate is used),

b) sedimenting the sample to obtain a purified sample substantially free of DNA, proteins and cellular components(see page 8, where the step of centrifugation is a form of sedimentation that will remove DNA, proteins and cellular components),

c) adding to the purified sample about an equal volume of a water soluble organic solvent to precipitate the purified RNA (See page 8, preferred embodiment 2, where the aqueous phase is precipitated with isopropanol),

d) sedimenting the precipitated RNA (see page 8, last sentence),

e) washing and solubilizing the precipitated RNA (see page 9, first five sentences).

With regard to claim 50, Chen teaches the use of chloroform (see page 8, middle of the page).

With regard to claim 51, Chen teaches addition of a composition which can be at "about 1.5 X" concentration (see page 8).

With regard to claim 52, 60, 61, Chen teaches precipitation with isopropanol (see page 8).

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claim 29-39, 41, 46-52 and 59-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al (Chinese patent 1,220,995, translation) in view of Chomczynski (U.S. Patent 5,346,994).

Chen teaches a *method for isolating purified RNA from a biological sample* of claims 29 and 59 (see page 3, bottom half, for example or page 4) comprising:

a) *treating the sample comprising phenol at a final concentration ranging from about 10% w/w to about 60% w/w and at least one ribonuclease inhibitor* (see page 6, where 12-46% phenol is used in conjunction with guanidine isothiocyanate, an RNAse inhibitor and see page 8, preferred embodiment 2, step 1, where the phenol reagent with 30% w/w is added to the tissue),

b) mixing the sample with at least one hydrophobic solvent and a buffer at a concentration sufficient to maintain a pH in the range from about pH 3.6 to below pH 4.0 (see page 8, preferred embodiment 2, where the pH of the phenol reagent is pH 3.5, which is about 3.6 and where the hydrophobic solvent chloroform/isoamyl alcohol is added to the solution. Further note that Chen teaches overlapping ranges of pH from 3.5 to 6.5 and the use of glacial acetic acid to regulate the pH value (see page 3)),

c) recovering the purified RNA from an aqueous phase to which about an equal volume of a water soluble organic solvent is added to precipitate the purified RNA (See page 8, preferred embodiment 2, where the aqueous phase is precipitated with isopropanol),

d) washing and solubilizing the precipitated RNA (see page 9, where the RNA precipitate is washed with alcohol and dissolved in a buffer).

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With regard to claims 31-34, Chen teaches the use of ribonuclease inhibitors (see page 8, preferred embodiment 2, line 1, where the chaotropic salt guanidine

isothiocyanate is used as an RNAse inhibitor at a concentration in the range of 0.5 M to about 6M).

With regard to claims 35-36, Chen teaches the use of detergents such as SDS and sarcosine including a range of 0.1% SDS (see page 8, preferred embodiment 2, lines 2-3).

With regard to claims 37-39, Chen teaches the use of sodium acetate and trisodium citrate, where claim 38 indicates that acetate is a preferred salt and claim 39 indicates that citrate is a preferred chelating agent).

With regard to claim 41, Chen teaches the use of Guanidine salts (see page 8, line 1).

With regard to claims 46, Chen teaches a pH range of 3.5-6.5 and exemplifies a pH of 3.5 (see page 3 and see page 8, preferred embodiment 2).

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With regard to claims 47-49, Chen teaches the steps of:

a) treatment with the monophase reagent comprising phenol in concentrations from 12-46% w/w (see page 6) with a pH from 3.5-6.5 (see page 3) and a chaotrope (see page 6 where guandine isothiocyanate is used),

b) sedimenting the sample to obtain a purified sample substantially free of DNA, proteins and cellular components(see page 8, where the step of centrifugation is a form of sedimentation that will remove DNA, proteins and cellular components),

c) adding to the purified sample about an equal volume of a water soluble organic solvent to precipitate the purified RNA (See page 8, preferred embodiment 2, where the aqueous phase is precipitated with isopropanol),

d) sedimenting the precipitated RNA (see page 8, last sentence),

e) washing and solubilizing the precipitated RNA (see page 9, first five sentences).

With regard to claim 50, Chen teaches the use of chloroform (see page 8, middle of the page).

With regard to claim 51, Chen teaches addition of a composition which can be at "about 1.5 X" concentration (see page 8).

With regard to claim 52, 60, 61, Chen teaches precipitation with isopropanol (see page 8).

While Chen teaches the use of a pH adjusting component, Chen does not state that the amount used will be sufficient to maintain pH.

Chomczynski teaches the use of a pH adjusting component in an RNA solvent solution where "the solvent solution may include a buffering component, such as sodium acetate or sodium citrate, in an amount sufficient to maintain the pH of the solution (see column 3, lines 17-22)."

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the isolation buffer of Chen, who notes a desire to "regulate the pH value (see page 3)", to incorporate enough buffering component as

taught by Chomczynski since Chomczynski notes "the solvent solution may include a buffering component, such as sodium acetate or sodium citrate, in an amount sufficient to maintain the pH of the solution (see column 3, lines 17-22)." An ordinary practitioner would have been motivated to include sufficent buffering in the isolation buffer of Chen in order to maintain the pH since both Chen and Chomczynski teach and motivate the use of buffering components to maintain the pH of the solution.

6. The rejection of claims 48-51 under 35 U.S.C. 103(a) as being unpatentable over Chen et al (Chinese patent 1,220,995, translation) in view of Focus (1998) 20(2):36 is moot in view of the cancellation of new matter, which makes Chen anticipatory again.

Claim Rejections - 35 USC § 112

7. The rejection of claims 47-51 under 35 U.S.C. 112, first paragraph is moot in view of the deletion of this language.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 29-39, 41, 46-52 and 59-61 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for to prepare purified RNA which does not reveal the presence of DNA by RT-PCR when a pH of 3.8, 40% phenol, 4M guanidine, 5% glycerol, 0.1% sarcosine and 10 mM sodium citrate, does not

reasonably provide enablement for conditions with a pH other than 3.8 or different reagent concentrations are used. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a method of purifying RNA. The invention is in an class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims encompass methods using reagents with phenol concentrations from 10-60% with a pH from "about" 3.6 to below 4.0. The claims thus clearly encompass a pH of 3.5, which is the necessary meaning of "about 3.6" as well as a variety of reagent conditions.

Quantity of Experimenation

The quantity of experimentation in this area is large since there is significant variability in the purification efficiency.

The unpredictability of the art and the state of the prior art

Applicant's own declaration, filed January 17, 2007, demonstrates that certain conditions do not function. Applicant notes that Chen's use of pH 3.5 did not function to purify RNA to a level where the contaminating DNA was not detectable by RT-PCR. This demonstrates that at least one embodiment within the scope of the claims does not function. This unpredictability is heightened by Applicant's specification, which shows that a pH of 4.2 apparently also functions, which is outside the claimed range (see example 6) and only shows the pH of 3.7 and 3.8 functioning within the claimed range (see examples 1-5). Thus, given Applicant's arguments and evidence, it is entirely unpredictable which components will yield RNA that is free of DNA contamination detectable by RT-PCR within the range of the elements claimed.

Working Examples

The specification has working examples at pH 3.7 and 3.8, but does not enable the entire range claimed. Further, the specification utilizes only 40-50% phenol concentrations in the examples at pH values below 4.0. Thus, the working examples are not commensurate in scope with the claims.

Guidance in the Specification.

The specification does not provide any guidance why pH 3.5 should fail to function while pH 3.7 and 3.8 should function.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the level of unpredictability evidenced by Applicant's declaration is opposed to patentability. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the full scope of the claims and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Allowable Subject Matter

10. Claims 44, 62 and 63 are allowed.

11. The following is a statement of reasons for the indication of allowable subject matter: Claims 62 and 63 are drawn to the use of particular phenol derivatives or particular organic compounds in the RNA isolation buffer. The search did not identify any prior art which taught or suggested the use of the specific chemical compounds listed in RNA (or nucleic acid) isolation. With regard to claim 44, while Puissant teaches the pretreatment step with Guanidine, Puissant never suggests a pH of less than 4.0.

Response to Arguments

12. Applicant's arguments filed September 4, 2007 have been fully considered but they are not persuasive.

Applicant argues that Chen does not meet the newly claimed requirement that the purified RNA lacks DNA as assayed by RT-PCR. Applicant has evidenced this fact in the declaration filed January 17, 2007. The problem with this argument is that the claims are not commensurate in scope with the declaration. This is particularly a problem since Chen literally teaches embodiments which fall within the scope of the claims. The declaration indicates that the conditions used by Dr. Chomczynski were those of example 1 of the specification. This example used particular embodiments with a pH of 3.8, 40% phenol, 4M guanidine, 5% glycerol, 0.1% sarcosine and 10 mM sodium citrate. Thus, for these conditions, there is undoubtedly an unexpected result relative to Chen regarding the presence of DNA. However, this example does not provide support that other conditions, such as pH 3.5, which must literally be within the scope of "about pH 3.6", if anything is, or other reagent conditions, will achieve the same results. Thus, the claims are not commensurate in scope with the declaration.

As MPEP 716.02(d) notes "the "objective evidence of nonobviousness must becommensurate in scope with the claims which the evidence is offered to support." In this case, the objective evidence that Chen would not function would also support an argument that the claimed invention is not fully enabled. Therefore, the new scope of enablement rejection is made in view of Applicant's amendment.

Conclusion

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jeffrey Fredman
Primary Examiner
Art Unit 1637
9/17/07